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UNDERNUTRITION AS AN UNDERLYING CAUSE OF MALARIA MORBIDITY AND MORTALITY IN CHILDREN LESS THAN FIVE YEARS OLD

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Abstract. Undernutrition is highly prevalent in many areas in which morbidity and mortality from malaria is unacceptably high. That undernutrition exacerbates diarrhea and respiratory infections is widely demonstrated; however, research suggests that it may exacerbate, palliate, or have little effect on malaria outcomes. This review examines the global burden of malaria associated with various nutrient deficiencies as well as underweight status in children 0–4 years of age. Although the association is complex and requires additional research, improved nutritional status lessens the severity of malaria episodes and results in fewer deaths due to malaria. Deficiencies in vitamin A, zinc, iron, folate, as well as other micronutrients are responsible for a substantial proportion of malaria morbidity and mortality. It is recommended that nutrition programs be integrated into existing malaria intervention programs.

INTRODUCTION

Malaria is a major cause of morbidity and mortality in tropical and subtropical regions. Malaria often afflicts populations that are both impoverished and malnourished, and a large portion of the burden of malaria falls upon the most vulnerable within the population, children and pregnant women.[1] A variety of interventions are used to combat malaria, including insecticide-treated bed nets, environmental control, chemoprophylaxis, and prompt, appropriate case management.[2] There exists no single solution or program to combat malaria, rather a comprehensive approach is required with concurrent interventions on many levels.

Nutrition plays a major role in maintaining health, and malnutrition appears to generate vulnerability to a wide variety of diseases and general ill health.[3,4] Opinions are mixed regarding how undernutrition, whether it is characterized in terms of growth faltering or micronutrient malnutrition, affects susceptibility to malarial illness and mortality. Historical observational studies provide some evidence of harm resulting from adequate nutrition,[5–10] whereas more recent studies indicate either no evidence of benefit or some benefits resulting from nutritional adequacy.[1,11,12] Animal studies suggest that improved nutritional status is protective against malaria, but consensus has yet to be reached regarding its effects in human populations.[1] The purpose of this paper is to review the evidence from recent epidemiologic work on undernutrition as an underlying cause of malaria morbidity and mortality in children less than five years of age, and to highlight areas in which further research is required. The paper will review published research both on underweight or growth faltering in children, as well as particular micronutrient deficiencies that are considered relevant to the malaria-malnutrition association: iron, zinc, and vitamin A.

Underweight. Undernutrition is considered to be the underlying cause of more than 50% of all childhood deaths in the world.[13] Undernutrition diminishes the ability of all systems of the body to perform properly, with particularly grave consequences in young children. The relationship between underweight status and ill health, however, is complex because ill health often results in undernutrition and undernutrition increases susceptibility to disease, particularly severe disease. Numerous studies have demonstrated associations between undernutrition and growth retardation, impaired mental development, and increased susceptibility to infectious diseases.[14–19]

Because children are growing, it is heuristic to characterize their overall nutritional status by comparing their growth or attained weight or height for their age (and sex) with that of a reference population of generally healthy children. This comparison is calculated in terms of standard deviation scores or z-scores in which the placement of a measure (in this case a child's weight) within a distribution (the reference weights of healthy children) is characterized by its distance from the median in standard deviation (SD) units.[20] Z-scores at the lower end of the distribution are typically categorized in nutritional terms as mild (−1.01 to −2.00 SD), moderate (−2.01 to −3.0 SD), or severe (<−3.0 SD) undernutrition because they are only infrequently found in generally healthy children. For example, we would expect that only 0.1% of healthy children to have a z-score < −3 SD and only 2.2% of healthy children to have a z-score between -2 and −3 SD. The World Health Organization (WHO) maintains a global database on child growth and malnutrition to calculate the prevalence of undernutrition among children less than five years of age for each of the 14 WHO mortality regions.[21,22] Weight-for-age is used to assess underweight as an indicator of undernutrition because of its availability and its ability to capture both stunting (generally associated with long-term undernutrition) and wasting (manifestation of recent and acute undernutrition). As shown in Table 1, the regions with the highest prevalences of undernutrition (weight-for-age z-score < −2 SD) in children less than five years of age are found in Southeast Asian regions B and D (26% and 46%) and African regions D and E (32% and 31%). These are also the regions, especially in Africa, with high malaria burdens.[23]

Children who are underweight are thought to have increased susceptibility to malaria for a variety of reasons, most notably through a reduction in the function of the immune system. When a child is undernourished, he or she may be unable to mount an appropriate immune response to the malaria parasite due to reduction in T lymphocytes, impairment of antibody formation, decreased complement formation, and atrophy of thymus and other lymphoid tissues, among others.[24]

Early observational studies suggested a protective effect of undernutrition against malarial morbidity and mortality.[5–8,10] Subsequently, a plethora of animal studies were conducted to

TABLE 1

Prevalence (%) of underweight and micronutrient deficiencies in children less than five years old in regions of the world in which malaria is a public health problem[23,37,69,88]*

Region	Weight-for-age z-score (%)			Anemia	Zinc deficiency	Vitamin A deficiency
	<–3	–3 to –2	–2 to –1			
AFR-D	7	25	38	60	37	28
AFR-E	7	24	38	60	62	35
EMR-D	5	20	38	63	52	23
SEAR-B	5	21	38	49	34	48
SEAR-D	13	33	36	66	73	30
WPR-B	2	14	34	49	9	14

* In a generally healthy population, the expected prevalences of weight for age z-scores <–3, –3 to –2 and –2 to –1 SD are 0.1%, 2.2%, and 13.6%, respectively. AFR-D = Algeria, Angola, Benin, Burkina Faso, Cameroon, Cape Verde, Chad, Comoros, Equatorial Guinea, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Madagascar, Mali, Mauritania, Mauritius, Niger, Nigeria, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, and Togo; AFR-E = Botswana, Burundi, Central African Republic, Congo, Cote d'Ivoire, Democratic Republic of the Congo, Eritrea, Ethiopia, Kenya, Lesotho, Malawi, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Uganda, United Republic of Tanzania, Zambia, and Zimbabwe; EMR-D = Afghanistan, Djibouti, Egypt, Iraq, Morocco, Pakistan, Somalia, Sudan, and Yemen; SEAR-B = Indonesia, Sri Lanka, and Thailand; SEAR-D = Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Maldives, Myanmar, and Nepal; WPR-B = Cambodia, China, Cook Islands, Fiji, Kiribati, Lao People's Democratic Republic, Malaysia, Marshall Islands, Micronesia (Federated States of), Mongolia, Nauru, Niue, Palau, Papua New Guinea, Philippines, Republic of Korea, Samoa, Solomon Islands, Tonga, Tuvalu, Vanuatu, and Viet Nam.

resolve whether protein-energy malnutrition exerted protective effects against malaria morbidity and mortality. Although a number of studies concluded that protein-deprived animals experience less morbidity and mortality due to malaria, there was also evidence that the protein-deprived animals were also less able to clear the infection and to develop less of an antibody response to the parasite.[1] Human studies conducted in resource-poor and famine environments have reported protective effects of undernutrition, assessed through clinical evaluations, autopsy reports, or refeeding programs.[5–9] More recent studies, however, have been unable to demonstrate a significant association between underweight status and malarial illness.[1,11,25] These discrepant results may be due to changing epidemiologic and anthropometric tools over time and the different populations studied. Earlier studies were primarily done in famine environments and evaluated the effect of refeeding of severely malnourished individuals. It is likely that the biologic effects of refeeding are different from those of food supplementation in less severely malnourished populations because of the delayed response of the immune system coupled with the speed of parasite recrudescence in the severely malnourished individual.

Recently, a series of analyses were conducted to obtain pooled estimates of the relationship between underweight and malaria morbidity and mortality across published studies (morbidity) or from extant data obtained from large prospective cohort studies (mortality).[23] This was done for the WHO Comparative Risk Assessment (CRA) project, which sought estimates of the relationships between various risk factors, including undernutrition, and morbidity and mortality by cause. Relevant studies were identified through database searches of literature published in English from 1966 to 2001, the articles cited by these studies, and researcher recommendation.[23]

From this search, two cohort studies provided data on the relationship between underweight and malaria morbidity. In The Gambia, anthropometry and blood samples were assessed in a group of children (n = 317) who were then followed throughout the rainy season. Children with higher weight-for-age were at a slightly higher risk of developing parasitemia, but this was not statistically significant.[26] Another study, conducted in Vanuatu where there is both *Plasmodium falciparum* and *P. vivax*, followed a much larger group of children (n = 1,511) and found that *P. vivax* malaria during the six-month period before assessment was strongly associated with acute malnutrition.[27] Data from these two cohort studies were combined to calculate a pooled relative risk of clinical malaria morbidity among children with weight for age z-scores < –2 SD. Children who were moderately to severely underweight were found to have an increased but not statistically significant risk of a clinical malaria attack as compared with those better nourished (1.31, 95% confidence interval [CI] = 0.92–1.88).

To estimate mortality risk, the investigators examined multiple degrees of undernutrition in three studies in which anthropometric status was ascertained, and children were followed prospectively for survivorship, and cause of death was determined using described verbal autopsy methods.[23,28–30] In Ghana, children 0–12 months of age were followed for 12 months resulting in 1,545 child-years of observation.[28] In Guinea-Bisseau and Senegal, children 0–59 months of age were followed for periods of six months, resulting in 15,593 and 7,133 child-years of observations, respectively.[29,30] Using analytic procedures pioneered by Pelletier and others,[13,17,31] the data were combined to calculate a pooled relative risk of malaria mortality among children with varying levels of undernutrition. Children with z-scores < –3.0 SD were 9.49 (95% CI = 3.25–27.66) times more likely to die, those with z-scores between –2 and –3 SD were 4.48 (95% CI = 2.20–9.15) times more likely to die, and those with z-scores between –1 and –2 SD were 2.12 (95% CI = 1.48–3.02) times more likely to die of malaria than children with z-scores > –1 SD.[23]

Based on these pooled relative risks and estimates of the prevalence of underweight, the fraction of malaria morbidity and mortality attributable to underweight could be calculated (population attributable risk or PAR) (Tables 2 and 3). The worldwide attributable risk fraction of malaria morbidity was 8.2% for weight for age < –2 SD, although again because the risk estimate was not statistically significant, the confidence interval around this estimate could include 0%, meaning no contribution of underweight to malarial morbidity. The PAR was 57.3% for malaria mortality due to low weight for age (weight for age < –1 SD). Combining the prevalence data and the attributable risk fractions, the investigators calculated that 549,200 malaria deaths were attributable to undernutrition in children less than five years of age.[23]

TABLE 2

Fraction of clinical malarial attacks in children less than five years old attributable to nutritional deficiencies[23,69,88]*

Region	Population attributable fraction (%)		
	Underweight <–2 Z-score	Zinc deficiency	Vitamin A deficiency
AFR-D	8.4	17.1	18
AFR-E	8.1	26.0	22
EMR-D	6.6	18.5	15
SEAR-B	6.8	3.0	27
SEAR-D	11.8	3.9	19
WPR-B	4.1	0.0	10
World	8.2	20.1	20

* For definitions of abbreviations, see Table 1.

TABLE 3
Malaria mortality in children less than five years old and fraction of deaths attributable to nutritional deficiencies[23,69,88]*

Region	Malaria deaths in children 0–4 years old (thousands)	Population attributable fraction (%)		
		Underweight	Zinc deficiency	Vitamin A deficiency
AFR-D	435.2	57.7	17.1	18.2
AFR-E	415.5	56.7	26.0	21.7
EMR-D	45.4	51.3	18.5	15.0
SEAR-B	3.3	52.0	3.0	30.3
SEAR-D	54.1	66.4	3.9	18.5
WPR-B	3.0	39.8	0.0	0.0
World	958.5	57.3	20.1	19.5

See Table 1 for countries in each region
* For definitions of abbreviations, see Table 1.

Since the underlying data for the relative risk estimate is based on cohort studies, this estimate is likely to be confounded by a number of factors, including previous malarial episodes, micronutrient deficiencies, poverty, and poor access to health care. When considered within the spectrum of underweight severities, there appears to be a risk gradient. The most underweight children have the highest risk of malaria mortality and risk decreases with improved underweight status as identified by z-scores. Although the highest risk is associated with the most severely underweight children, the burden of disease or death is greater for children with mild to moderate underweight status because of the high prevalence of children with mild to moderate underweight status in many countries. Therefore, one needs to develop interventions that assist not only the severely underweight children, but also tackle the full spectrum of undernutrition within the population.[16,23]

Iron-deficiency anemia. That iron deficiency adversely affects human health is widely recognized.[32–35] Iron plays a critical role in the transport of oxygen throughout the body and in cellular processes of growth and division. Iron deficiency results in a decrease in the hemoglobin concentration, which when sufficiently low is identified as anemia. In contrast, malaria causes anemia through cytokine-mediated suppression of hematopoeisis, and in addition, when infected with *P. falciparum*, the erythrocyte changes and becomes vulnerable to clearance.[36] Hookworm and other infections which cause blood loss also contribute to iron deficiency and anemia, often severe anemia.[37] All types of anemia, regardless of cause, reduce the oxygen transported throughout the body, and this leads to decreased productivity and increased risk of cardiovascular events.[38] Other poor health outcomes associated with iron deficiency and anemia include poor neurologic development in children, premature labor, low birth weight, and increased maternal and infant mortality.[32,33,35,38] Pregnant women are particularly susceptible to iron deficiency because of the increased demands on their iron stores by the developing fetus.[37]

Between two and five billion people worldwide are at least mildly iron deficient, making iron deficiency the most common micronutrient deficiency in humans today.[39,40] Iron deficiency is responsible for the majority of anemia worldwide, but in malaria-endemic regions, malaria may be responsible for the majority of child mortality due to severe anemia. Folate and vitamin A deficiencies have also been linked with anemia, although to a lesser degree.[41–43] The prevalence of anemia is often used to estimate the extent of iron deficiency in a population, even though in certain populations there may be other causes of anemia. As shown in Table 1, in malaria-endemic regions, the prevalence of anemia in young children ranges from 49% to 66%.[37] To obtain a conservative estimate of how much anemia is due to iron deficiency, one can measure the change in hemoglobin concentration or reduction in anemia over time with iron supplementation. Estimates range from 21% to 85% with an average of 51%.[44] A similar proportion of anemia was found to be alleviated with iron supplementation in clinical trials from malaria-endemic regions,[45] indicating similar beneficial hematologic effects from iron supplementation in both malaria endemic and non-malarious regions. This does not mean, however, that malaria is not a fundamental cause of the severe anemia observed in children in malaria-endemic areas. For example, a clinical trial in Tanzania compared malaria chemoprophylaxis with iron supplementation in infants, and demonstrated that both iron supplements and chemoprophylaxis reduced severe anemia, but chemoprophylaxis reduced severe anemia by 60% compared with 30% reduction in those receiving iron supplements.[46]

Despite the efficacy of supplementary iron for the prevention and treatment of iron deficiency and anemia, debates over the use of iron supplements in malaria-endemic regions continue because of concerns that they may increase susceptibility to malaria.

The nutritional immunity theory was developed from studies that observed a protective effect of iron deficiency on malaria severity.[47] The theory suggests that depriving the parasite of essential nutrients (iron, in particular) creates an uninhabitable internal environment, thus preventing the parasite from fully proliferating. In 1985, a study in mice found that the entire iron-replete group of mice infected with *P. chabaudi* died, whereas the iron-deficient mice were far less likely to die. When the iron-deficient mice were then fed iron-sufficient foods, they fell victim to recrudescent parasitemia.[48] More recent experimental evidence refutes the earlier nutritional immunity hypothesis and concludes no significant protection of iron deficiency in young rats.[49] Other evidence suggests that iron deficiency impairs immune responses, including T lymphocyte production and activity, natural killer cell activity, and neutrophil function.[50]

The authors of the WHO CRA report on iron[37] did not summarize findings across studies to examine the contribution of iron deficiency anemia to malaria disease burden. However, Shankar and others[51] conducted a meta-analysis of 12 published and unpublished placebo-controlled iron supplementation trials[7,46,52–61] to examine the effect of iron supplementation on malaria morbidity. The trials were identified through a keyword search in MEDLINE and on the internet using LYCOS, as well as citations within these articles and author recommendations. Overall, there was a significantly heightened risk of infection as measured at the end of the study associated with malaria and iron supplementation (1.17, 95% CI = 1.08–1.25). Iron supplementation appeared to increase other malariometric indices, including risk of a malaria attack (1.09, 95% CI= 0.92–1.30; 8 studies) and spleen enlargement (1.12, 95% CI = 0.99–1.26; 6 studies), although the increases were not significant. Thus, iron supplementation had the unintended consequence of marginally increasing certain malariometric indices in clinical trials. The hematologic

improvements in the iron supplementation groups summarized over the studies were significant and included an average increase in hemoglobin levels of 1.2 g/dL (95% CI = 1.2–1.3) and a 50% decrease in the risk of severe anemia (95% CI = 45–54%).[45] Consensus has not yet been reached on the risks and benefits associated with iron supplementation and malaria morbidity and mortality.[50] Although more research is indicated, current knowledge suggests that the alleviation of anemia through iron supplementation is likely to benefit all iron-deficient populations, including those in malaria-endemic regions.

Zinc deficiency. Zinc is a required element in basic biologic processes such as gene expression, and cellular growth and differentiation.[62] Due to the ubiquity of zinc in these basic processes, zinc deficiency can result in depressed immune function, growth faltering, and morbidity.[63,64] One of the first clinical signs of inadequate zinc is depressed immunity,[65] which may be reversed with zinc supplementation. A meta-analysis of zinc supplementation trials concluded that zinc deficiency contributes to growth faltering in young children in developing countries.[66] A number of clinical trials have examined the effects of zinc supplementation on the incidence of diarrhea and pneumonia in children, and a pooled analysis of the results of these clinical trials indicated that the control group experienced a significantly higher risk of disease compared with the zinc supplementation group.[67–69]

Although the importance of zinc for human health is widely recognized, estimating the burden of disease has been difficult due to inadequate tools with which to measure zinc deficiency.[70,71] Plasma zinc levels are commonly used to assess zinc deficiency, but this method is neither adequately sensitive nor specific due primarily to zinc homeostasis.[71] In response to this lack of readily available biomarkers, the International Zinc Nutrition Consultative Group developed a method to estimate the prevalence of zinc deficiency in a population by examining the availability of zinc in the local diet.[72] Using this method, the global prevalence of zinc deficiency has been found to range from 6% to 73% among WHO subregions, with an average prevalence of 31% worldwide.[69] As shown in Table 1, inadequate zinc intakes are highly prevalent in areas of the world affected by malaria. Given the high prevalence of zinc deficiency and the known role of zinc in immune function, it is important to consider whether zinc deficiency affects malarial morbidity and mortality.

Zinc deficiency decreases the ability of the body to respond to infection, affecting both cell-mediated immune responses and humoral responses.[65] B cell proliferation is less dependent on zinc than is T cell proliferation; however, zinc deficiency does result in fewer naive B cells available to produce antibodies to new antigens.[73] Zinc deficiency has also been hypothesized to exacerbate malaria and other diseases (infection with human immunodeficiency virus, and tuberculosis) that rely on macrophage killing of infected cells.[65]

As part of the acute phase response to infection, plasma zinc levels decrease as it is sequestered with metallothionein in the liver. Because zinc is a required nutrient for both the host and the parasite, this may be viewed as an adaptive response to deprive the parasite of required nutrients. However, it is important to bear in mind that despite decreased plasma zinc concentrations, the plasma concentrations remain well above any requirements of a parasite for replication.[65]

Numerous animal studies have demonstrated the role of zinc in the immune response to infectious disease.[65] Studies that investigated the relationship between zinc status and malaria also showed a protective effect of zinc supplementation. For example, zinc supplementation of mice during infection with *P. berghei* resulted in decreased markers of oxidative stress.[74] In addition, moderate zinc deficiency was found to result in 40% mortality from a traditionally non-lethal form of rodent malaria, *P. yoelii* (Shankar AH, unpublished data).

Using a MEDLINE keyword search, the Comparative Risk Assessment research team identified three trials that investigated the preventive effects of zinc supplementation on malaria morbidity and mortality in children.[75–77] In the Gambia (n = 110), children who received 70 mg of zinc supplementation twice a week for 15 months had 32% ($P = 0.09$) fewer malaria-related clinic visits than did the placebo group, but this was only marginally significant and the diagnostic criteria for malaria were not stated.[76] A randomized trial in Papua New Guinea (n = 274) found a 38% (3–60%) reduction in clinic visits for slide-confirmed malaria in the group that received 10 mg of elemental zinc supplementation six days a week for 46 weeks compared with a placebo group.[77] Finally, a randomized trial in Burkina Faso (n = 709) provided either placebo or 12.5 mg of supplemental zinc six days a week for six months, but did not show a difference in malarial illness between the two groups (0.98, 0.86–1.11).[75] They were, however, able to show a significant decrease in the prevalence of diarrhea in the zinc group (0.87, 0.79–0.95) suggesting that variation in zinc status did affect morbidity risk in the population. The Gambia and Papua New Guinea studies both used health center–based clinically-confirmed malaria episodes as their primary outcome of interest, whereas the Burkina Faso study incorporated household surveillance for fever along with the administration of the zinc supplements, and thus, was far more sensitive for identifying febrile days. However, in an area with a high background prevalence of parasitemia such as Burkina Faso, it is not clear how many were actually clinical malaria attacks. Furthermore, identification of these febrile days resulted in early treatment with anti-malarial drugs, potentially preventing more severe malarial illnesses.

Due to these differences in design, the Burkina Faso study was not considered comparable to the Gambia and Papua New Guinea studies and was dropped from a meta-analysis performed for the WHO CRA Project.[69] Combining the data from the Gambia and Papua New Guinea trials resulted in a pooled estimate of a 36% (9–55%) decrease in malaria episodes brought to the health centers in the zinc supplementation group. A relative risk of 1.56 (1.29–1.89) for health center malaria episodes in zinc-deficient young children was derived by calculating the inverse of the pooled odds ratio of the protective effect of zinc supplementation. In the absence of direct data, these risk estimates were extended to include deaths due to malaria as well. Based on the prevalences of inadequate zinc intake (Table 1) and the relative risk calculated from the pooled analyses, zinc deficiency in children 0–4 years old may be responsible for approximately 20% of malaria clinic attacks (Table 2) and 193,000 malaria deaths each year (Table 3).

Unlike many causes of death and disability, zinc deficiency is ultimately preventable with adequate support. Current intervention strategies focus on zinc supplementation, fortification of locally acceptable foods, and dietary modification to

consume greater amounts of animal products and fewer fiber and phytates. Given the public health importance of zinc deficiency, the development of effective programs to reduce zinc deficiency is of high priority.

Vitamin A. Vitamin A plays an essential role in the immune response and in eye health.[78] The dominant symptom of severe vitamin A deficiency is xerophthalmia, a major cause of blindness in Africa and Latin America that initially appears as night blindness and results in corneal ulceration and blindness if left untreated.[79] Severe vitamin A deficiency is rare and most vitamin A associated morbidity results from mild to moderate deficiency. Vitamin A supplementation has been shown to improve general eye health, as well as decrease measles, diarrhea, and all-cause mortality.[78–85]

There are a number of ways to measure prevalence of vitamin A deficiency.[78,79] Serum retinol concentrations are often used with a cut-off value of < 0.70 μmol/L. Serum retinol concentrations, however, have been observed to decrease as part of an inflammatory response even in vitamin A-sufficient individuals, a physiologic response that confounds the interpretation of associations between vitamin A status and malaria morbidity. The prevalence of xerophthalmia or corneal lesions in a population can also be used to infer the prevalence of deficiency in the population. Ideally, one would like to be able to determine how much vitamin A is stored in the liver, and there are isotope dilution techniques currently being developed for this purpose.[86,87] Regional prevalences have been calculated using existing country specific data on the prevalence of vitamin A deficiency determined by serum retinol concentration and clinical eye signs (Table 1).[88] As shown, vitamin A deficiency is common in malaria-endemic regions of the world.

Vitamin A plays an essential role in the proper functioning of the immune system and is believed to be necessary for host resistance to malaria, although early animal studies suggested that deficiency was protective.[1] In 1946, a study of vitamin A-deficient chicks indicated severe vitamin A deficiency was associated with slightly milder infection with malaria compared with well nourished chicks, while the same experiment with ducks was unable to demonstrate an association.[89] Later studies in rats indicated that vitamin A deficient rats were significantly more susceptible to the rat malaria parasite *P. berghei* than were those rats with adequate vitamin A intake.[90] Follow up studies, however, were less convincing and only able to demonstrate increased susceptibility to malaria in those rats with very severe vitamin A deficiencies that began when the rats were very young.[91] Overall, animal studies suggest that vitamin A deficient animals are more vulnerable to malaria morbidity and mortality.

The hypothesized mechanism through which vitamin A mediates susceptibility to malaria is increased phagocytosis of parasitized erythrocytes and reduced proinflammatory cytokine responses to infection. Vitamin A may assist in the upregulation of CD36 expression, which aids in phagocytosis and may activate substances (peroxisome proliferators-activated receptor), which inhibit the inflammatory responses associated with severe and cerebral malaria.[92]

Cross-sectional studies suggest an inverse relationship between plasma retinol concentrations and increased malaria parasitemia,[93–98] but the causality of the association is uncertain. More definitive causal evidence on vitamin A and malaria would come from randomized controlled trials, but as of 2001, only two clinical trials of vitamin A supplementation had been conducted in regions with endemic malaria, according to an extensive keyword search performed using MEDLINE, as well as a variety of other published and unpublished material.[99–101] A clinical trial in Papua New Guinea found a significantly lower risk of malaria morbidity in the vitamin A group compared with the placebo group (0.70, 0.57–0.87).[99] A clinical trial in Ghana found no association between vitamin A supplementation and malaria morbidity (1.03, 0.74–1.43) or mortality (1.03, 0.74–1.43); however, this study did not have the statistical power to detect a difference of less than 70% between the two groups.[100,102]

For the purposes of the WHO CRA project, the relative risk of malaria attributable to vitamin A deficiency was calculated by taking the inverse of the protective effect seen in the Papua New Guinea study.[88] After combining the risk estimates with vitamin A prevalence data, the PAR of malaria morbidity and mortality for vitamin A was calculated (Tables 2 and 3). The fraction of malaria morbidity attributable to vitamin A deficiency was determined to be 20% worldwide. More than 90% of the 187,000 malaria deaths worldwide attributable to vitamin A deficiency occur in Africa.[88]

Current intervention strategies include supplementation, fortification of a variety of foods, and education regarding the importance of vitamin A rich foods in the diet.

Other nutritional factors. There are a number of other micronutrients that play a role in the immune system and have been associated with malaria incidence. These include folate, long-chain polyunsaturated fatty acids, antioxidants, riboflavin, and thiamine.[1] Of these, folate has often been studied because of the role folate plays in the mode of action of some types of antimalarial drugs. Sulfadoxine plus pyrimethamine (SP) works primarily through the interruption of folate metabolism in the parasite and is commonly used in areas in which chloroquine resistance has spread. Mutations can cause the parasite to become less sensitive to antifolates such as SP, inducing resistance. In addition, some lines of *P. falciparum* are able to access exogenous folate and thus circumnavigate the blocked folate synthesis mechanism.[103] Folate supplementation is provided widely in antenatal programs in developing countries to prevent and treat anemia.[40] Folic acid also plays a major role in cell mediated immunity, as well as DNA and protein synthesis in general. Initial studies of folic acid supplementation demonstrated decreased anemia in the folic acid supplementation group, and there was no sign of interference with anti-malarial activity of pyrimethamine.[104] However, a recent clinical trial in The Gambia examining the effects of chloroquine and SP treatments in conjunction with iron and folic acid supplementation found that folic acid supplementation significantly increased SP treatment failure rate ($P = 0.04$), while iron supplementation was not associated with increased prevalence of malaria.[105] The precise biologic mechanism through which folic acid supplementation interferes with SP treatment remains to be identified. Improving the folic acid status of women to prevent anemia and neural tube defects is undisputedly necessary; yet questions remain regarding the effect folic acid supplementation has on the effectiveness of anti-folates used in malaria treatment.

Fatty acids are thought to be toxic to *P. falciparum* and deficiency should be corrected.[106,107] Deficiencies of antioxidants like vitamins E and C, however, appear to damage the parasite through increased exposure to oxygen radicals and

may therefore be protective to the host.[108] Along the same vein, deficiency of riboflavin may also be protective for the host because it encourages oxidative activity which is harmful for the parasite.[109–111] However, recently published studies have put into question the theory that a reduction in antioxidants is protective. A longitudinal study in Uganda found that children with acute malaria have depressed plasma concentrations of antioxidants.[112] In addition, scientists in Gabon used high-performance liquid chromatography to determine riboflavin levels in acute malaria cases and were unable to find an association between riboflavin deficiency and parasitemia.[113] Finally, with regard to thiamin, an observational study concluded that deficiency was associated with more severe infections, cerebral malaria in particular.[114]

The relationship between malarial illness and nutrition is undeniably complex. Additional effort must be put into elucidating the contributions of each micronutrient, both individually and in combination, with regard to malaria.

DISCUSSION

Existing evidence strongly suggests that micronutrient deficiencies and general undernutrition increase the burden of malaria morbidity and mortality. Attributable fractions calculated by the CRA project[23,69,88] demonstrate that large numbers of children less than five years old suffer and die of malaria due to nutritional inadequacies in terms of protein energy, zinc, and vitamin A. These numbers can be interpreted in a very hopeful fashion because these illness episodes and deaths are entirely preventable with appropriate nutritional interventions. Available evidence suggests that iron supplementation programs may result in no or a small increased risk of malarial illness, but this must be verified and weighed against the known benefits of preventing and treating anemia. Overall, contrary to previously held beliefs that the undernourished individual is an unattractive host for the parasite, it seems that a well-nourished individual is better able to mount an immune response and is more capable of withstanding and clearing infection.

Susceptibility to malaria among famine victims that are in a refeeding program may, however, be a problem. The evidence indicates that refeeding famine victims enables multiplication of the parasite more quickly than it restores the resistance of the individual, leading to parasite recrudescence. In famine relief, it is recommended that malaria chemoprophylaxis is provided at the time of refeeding and that the population is monitored carefully for malaria and provided with appropriate treatment.

The calculation of population-attributable fractions requires two pieces of information: the prevalence of the exposure and the strength of the association between the exposure and outcome (relative risk). Clearly, the strength of the estimates relates to our confidence in the estimation of each component. Prevalence estimates of undernutrition are difficult to obtain for all regions of the world, but WHO has made a tremendous effort to provide the best possible estimates to date of low weight-for-age. Quantifying the extent of micronutrient deficiencies is more problematic because of the absence of appropriate indicators for quantifying prevalence (particularly for zinc), the confounding influence of other factors influencing the indicators (for vitamin A, zinc, and iron), and the added difficulties of conducting large-scale biochemical surveys in developing countries. The prevalences reported here represent the best estimates of the magnitude and distribution of vitamin A, iron, and zinc deficiencies available at this time. The prevalence of zinc deficiency is particularly speculative, and research is urgently needed to identify appropriate indicators for assessing zinc status in populations. The diagnosis of malaria mortality or morbidity is notoriously non-specific, particularly in endemic areas with year-round transmission, indicating a research need for better diagnostic tools. Although the authors of the CRA reviewed studies with similar definitions, subtle differences may have resulted in biased estimates of the relative risks. More concerted effort to reach consensus on definitions of malaria morbidity and to use them in future studies is necessary if we are to refine our estimates of the malaria burden attributable to undernutrition. Finally, it is important to consider that the relative risk estimates are pooled over a small number of studies, three cohort studies for undernutrition, and 1–2 controlled trials for vitamin A and zinc. It is only through additional research, involving randomized trials of nutritional interventions in malarious regions that we will be able to further calibrate the magnitude of these relationships.

It may be noted that we have considered these nutritional deficiencies as distinct entities, although they commonly are found in the same individuals. Much of the data summarized in the CRA come from published and unpublished randomized controlled trials of micronutrient supplements, and thus estimate the risk associated with each individual risk factor. For example, although underweight individuals may also be vitamin A deficient, the converse may not be true, in that one need not be underweight to be vitamin A deficient. Therefore, the effects of underweight status and vitamin A deficiency are relatively independent. This independence is confirmed in vitamin A supplementation trials that found mortality reductions with Vitamin A in both poorer and better nourished children.[82,83] Because zinc deficiency contributes to growth faltering, there may be some overlap of the risks from underweight and zinc deficiency,[66] although it is important to point out that zinc supplementation has been effective in reducing infectious disease in children independent of their overall nutritional status as characterized by weight or height.[67,68]

In summary, the evidence suggests that improving nutritional status of young children in multiple ways may reduce malaria morbidity and mortality, and should be considered within the packet of interventions to reduce the global burden of disease due to malaria. Careful evaluations of nutrition programs in malaria-endemic areas are needed to confirm this. Although treated separately in terms of estimating disease burden, improving nutritional status should follow an integrated approach, tackling both growth faltering and micronutrient deficiencies at the same time, and considering behavioral approaches as well as supplementation and fortification. The ultimate impact of integrated nutrition programs on malaria morbidity and mortality remains to be tested. However, regardless of their effect on malaria, such programs are important for reducing growth faltering and deaths in young children due to other causes such as diarrhea and pneumonia, and the beneficial externalities of nutrition programs likely extend to human capital formation, adult work capacity, and overall quality of life.

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